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PREFLIGHT HYPOXIC CHALLENGE TESTING: NEW IMPLICATIONS IN THE PEDIATRIC SETTING

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Son Espases hospital universitari

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PhD in Translational Research in Public Health and High Prevalence Diseases

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Doctor by the Universitat de les Illes Balears

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I hope readers enjoy reading my work.

Sebastian

Linz, Tuesday, November 10, 2020

"Life is what happens to you while you're busy making other plans"

John Lennon quote from the Song *"Beautiful Boy (Darling Boy)"* released in 1980

Thesis by compendium of publications

Research Project 1.

Peña-Zarza, J. A., Osona, B., Sailer, S., Gil-Sanchez, J. A. & Figuerola Mulet, J. Assessing hypoxia risk during air travel after a severe asthma exacerbation in children. Ann. Allergy, Asthma Immunol. 119, (2017). doi: 10.1016/j.anai.2017.07.034

Research Project 2.

Sailer, S., Osona, B., Gil-Sanchez, J.A., Bover Bauzà, C., Vetter-Laracy, S. & Figuerola Mulet, J. Assessment of portable oxygen concentrators in infants undergoing hypoxic challenge testing. A randomised controlled crossover trial. Acta Paediatr. Int. J. Paediatr. (2020). doi:10.1111/apa.15242

ABSTRACT / RESUMEN / RESUM

ABSTRACT

The number of passengers travelling on commercial aircrafts is steadily increasing, as are the numbers of air travelers in infancy and early childhood. Inflight medical emergencies are rare, but up to 10% of them occur in these young passengers. This situation will challenge physicians giving evidence-based recommendations concerning flight safety, especially in patients suffering from chronic respiratory, cardiac, neuromuscular or hematological diseases. Barometric pressure (Pb) and PaO_2 decrease in altitude. Therefore, at cruising altitude of 9000-13000 m aircraft cabins are pressurized to a cabin altitude of 2438 m, which is equivalent to breathing at a fraction of inspired oxygen (FiO2) of 0.15. Under normal health conditions this hypoxic state does not cause symptoms because it is compensated by increased respiratory minute volume and cardiac output, which maximize alveolar oxygen tension. Patients with compromised health conditions may show impaired hypoxic response. Different tests have been used to assess inflight hypoxia risk; the *British Thoracic Society (BTS)* guidelines continue to recommend hypoxic challenge testing (HCT), which introduces nitrogen into a whole-body plethysmograph cabin to reduce the FiO_2 from 0.21 to 0.15, simulating inflight conditions. The oxygen supply required by the subject is titrated.

This doctoral thesis includes 2 Research Projects related to HCT.

Research Project 1. — "HCT and Bronchial Asthma": Asthma is a highly prevalent disease and therefore a major public health issue, but there is no evidence for inflight hypoxic risk after acute asthma exacerbation in pediatric patients. We included 51 patients who required hospitalization due to severe exacerbation and performed HCT at 24 hours after oxygen removal. Patients who remained with arterial oxygen saturation (SaO_2) > 90% passed HCT and were considered fit to fly. Pre-enrollment spirometry was performed. Patients who failed HCT within the first 24 hours showed lower FEV1 values compared to the group who passed HCT. After 48 hours without oxygen all of the children (100%) passed the test. According to our results children hospitalized for asthma exacerbation who are able to breathe without oxygen therapy for 48 hours are fit to fly.

Research Project 2. — "HCT and Portable Oxygen Concentrators (POCs)": The gold standard of onboard oxygen supply in terms of effectiveness and safety remains unclear. In 2016 the *US Federal Aviation Administration (FAA)* approved the onboard use of POCs for oxygen supply but there is a lack of evidence supporting POC use in airplanes at cruising altitude, especially in passengers in the pediatric age range. We tested the effectiveness of continuous-POC (cPOC) vs. pulsed-flow POC (pPOC) during HCT. Twenty-two former preterm (ex-preterm) infants were enrolled in a randomized crossover study. Oxygen was administered through a POC in case of $SaO_2 \leq 85\%$. Immediate hypoxia reversal was achieved in all cases, demonstrating the effectiveness of POCs to revert HCT-induced hypoxia and the ability of pPOC to detect patient inspiration even in ex-preterm infants. Pediatric flight safety should be considered a public health issue that requires more intensive, specialized research to support guidelines.

RESUMEN

El número de pasajeros tanto adultos como pediátricos está aumentando constantemente. Las emergencias médicas durante el vuelo son poco frecuentes, pero hasta un 10% ocurren en niños. Un hecho que será en el futuro un desafío para los médicos al tener que dar recomendaciones basadas en la evidencia con respecto a la seguridad durante el vuelo, especialmente en pacientes con enfermedades crónicas de origen respiratorio, cardíaco, neuromuscular o hematológico. La presión barométrica y la presión arterial de oxigeno disminuyen en altitud. Por esta razón, los aviones (altitud de crucero 9000-13000 metros) están presurizados a una altitud de cabina de 2438 metros, equivalente a respirar FiO_2 0.15. En condiciones normales de salud, este estado de hipoxia no causa síntomas debido al aumento del volumen de minuto respiratorio y el gasto cardíaco, lo que maximiza la presión alveolar de oxígeno. Los pacientes con enfermedades crónicas pueden mostrar una respuesta patológica a la hipoxia. Existen diferentes pruebas para evaluar el riesgo de hipoxia durante el vuelo. El método recomendado según las pautas de *British Thoracic Society (BTS)* sigue siendo el test de hipoxia (Hypoxic Challenge Testing - HCT) introduciendo nitrógeno en una cabina de pletismógrafía reduciendo la FiO_2 de 0.21 a 0.15 simulando las condiciones durante vuelo y valorando el suministro de oxígeno requerido.

Esta tesis doctoral incluye 2 proyectos de investigación relacionados con HCT.

1. Proyecto de investigación: HCT y asma bronquial: El asma es una enfermedad de alta prevalencia y, por lo tanto, un problema mayor de salud pública, pero no hay evidencia de riesgo de hipoxia durante el vuelo después de una exacerbación aguda en pacientes pediátricos. Realizamos HCT en pacientes hospitalizados después de una exacerbación grave a las 24 horas de la retirada de oxígeno suplementario. Los pacientes que se mantuvieron con una SaO_2 > 90% superaron el HCT y se consideraron "aptos para volar". Se reclutaron 51 niños. Antes de iniciar HCT se realizó una espirometría. Los pacientes que fallaron HCT en las primeras 24 horas mostraron valores más bajos de FEV1. Después de 48 horas sin oxígeno, todos ellos (100%) pasaron la prueba. Según nuestros resultados concluimos que los niños hospitalizados por exacerbación asmática, son aptos para volar cuando están 48 horas sin precisar oxígeno suplementario.

2. Proyecto de investigación: HCT y concentradores de oxígeno portátiles (COPs). El gold standard del suministro de oxígeno a bordo de un avión en términos de efectividad y seguridad sigue siendo poco claro. En 2016, la *Administración Federal de Aviación* (FAA, por sus siglas en inglés) aprobó el uso a bordo de COPs para el suministro de oxígeno, pero no existe evidencia sobre su uso en altitud de crucero, especialmente en niños. Probamos la efectividad del rendimiento de los COPs (flujo continuo vs. pulsado) realizando HCT. 22 recién nacidos prematuros se incluyeron en un estudio cruzado aleatorizado. En el caso de $SaO_2 \leq 85\%$, el oxígeno se administró a través de COP. Se logró una reversión inmediata de la hipoxia en todos los casos, lo que demuestra la capacidad de los COP para revertir la hipoxia inducida por HCT y para detectar la inspiración del paciente (COP flujo pulsado) incluso en lactantes ex-prematuros.
En el futuro, la seguridad durante el vuelo en edad pediátrica debe considerarse como un problema de salud pública requiriendo una intensificación de la investigación en este campo específico.

RESUM

El nombre de passatgers, adults i pediàtrics, que viatgen en avions comercials està augmentant constantment. Les emergències mèdiques durant el vol són poc freqüents, però fins a un 10% ocorren en nens. Un fet que desafiarà en el futur als metges per donar recomanacions basades en l'evidència pel que fa a la seguretat durant el vol, especialment en pacients amb malalties cròniques d'origen respiratori, cardíac, neuromuscular o hematològic. La pressió baromètrica i la pressió arterial d'oxigen disminueixen en altitud. Per aquesta raó, els avions (altitud de creuer 9.000-13.000 metres) estan pressuritzats una altitud de cabina de 2438 metres, equivalent a respirar FiO_2 0.15. En condicions normals de salut, aquest estat d'hipòxia no causa símptomes per l'aument del volum de minut respiratori i la despesa cardíaca, el que maximitza la pressió alveolar d'oxigen. Els pacients amb malalties cròniques poden mostrar una resposta hipòxica patològica. Hi ha diferents proves per avaluar el risc d'hipòxia durant el vol. La manera més recomanable segons les pautes *British Thoracic Society (BTS)* segueix sent el test d'hipòxia (Hypoxic Challenge Testing - HCT) introduint nitrogen en una cabina de pletismografia reduint la FiO_2 de 0.21-0.15 simulant les condicions durant vol i valorant el subministrament d'oxigen requerit.

Aquesta tesi doctoral inclou 2 projectes de recerca relacionats amb HCT.

1. Projecte de recerca: HCT i asma bronquial: L'asma és una malaltia d'alta prevalença i, per tant, un problema major de salut pública, però no hi ha evidència de risc de hipòxia durant el vol després d'una exacerbació aguda en pacients pediàtrics. Realitzem HCT en pacients hospitalitzats després d'una exacerbació greu a les 24 hores de la retirada d'oxigen suplementari. Els pacients que es van mantenir amb una SaO_2> 90% van superar la HCT i es van considerar "aptes per volar". Es van reclutar 51 nens. Abans d'iniciar HCT es va realitzar una espirometria. Els pacients que va fallar HCT en les primeres 24 hores van mostrar valors més baixos de FEV1. Després de 48 hores sense oxigen, tots ells (100%) van passar la prova. Segons els nostres resultats concloem que els nens hospitalitzats per exacerbació asmàtica, són aptes per a volar quan estan 48 hores sense precisar oxigen suplementari.

2. Projecte d'recerca: HCT i concentradors d'oxigen portàtils (COPs). El gold standard del subministrament d'oxigen a bord en termes d'efectivitat i seguretat continua sent poc clar. En 2016, *l'Administració Federal d'Aviació* (FAA, per les sigles en anglès) va aprovar l'ús a bord de COPs per al subministrament d'oxigen, però no hi ha evidència sobre el seu ús en altitud de creuer, especialment en nens. Vam provar l'efectivitat del rendiment dels COPs (flux continu vs. premut) realitzant HCT. 22 nadons ex-prematurs es van incloure en un estudi creuat aleatoritzat. En el cas de $SaO_2 \leq 85\%$, l'oxigen es va administrar a través de COP. Es va aconseguir una reversió immediata de la hipòxia en tots els casos, el que demostra la capacitat dels COP per revertir la hipòxia induïda per HCT i per detectar la inspiració del pacient (COP flux premut) fins i tot en lactants ex-prematurs. En el futur, la seguretat durant el vol en edat pediàtrica s'ha de considerar com un problema de salut pública requerint una intensificació de la recerca en aquest camp específic.

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ABBREVIATIONS & ACRONYMS

COPD: Chronic Obstructive Pulmonary Disease

ft: feet

FEV1: forced expiratory volume in 1 second

FiO_2: fraction of inspired oxygen

FVC: forced vital capacity

HCT: hypoxic challenge testing

HR: heart rate

m: meters

Pb: barometric pressure

PO_2: partial pressure of oxygen

PaO_2: arterial partial pressure of oxygen

PAO_2: alveolar partial pressure of oxygen

$PACO_2$: alveolar partial pressure of carbon dioxide

cPOC: continuous-flow portable oxygen concentrator

pPOC: pulsed-flow portable oxygen concentrator

SaO_2: arterial oxygen saturation

RATIONALE

1 RATIONALE

In 2017 over 4.1 billion passengers travelled on commercial aircrafts, a number which is steadily increasing with predictions of up to 8.2 billion air travelers in 2037 according to the *International Air Transport Association (IATA)* forecast. This implies an increase in the number of passengers in infancy and early childhood.[1] A fact that will challenge physicians giving evidence-based recommendations concerning flight safety, especially in patients suffering from chronic respiratory, cardiac, neuromuscular or hematological diseases.[2]

1.1 INFLIGHT MEDICAL EMERGENCIES (IME)

Epidemiologic research currently offers a poor amount of data due to a lack of standardized reporting.[3] Global incidence of IME is estimated at 44000 cases/year, a number that is likely to increase as more passengers travel by air each year.[4,5] Data availability on pediatric IME (pIME) is even poorer. pIME comprise about 9-12% of all IMEs and demographic data reveals an average age of about 7 years.[6,7,8,9,10] *Rotta et al.* estimated that about 0.13% of all pIMEs resulting in death (fatal pIMEs) with a median subject age of 3.5 months and 90% being younger than 2 years (lap infants). In this cohort study most of the subjects showed a preexisting medical condition. [6] *Moore et al.* assessed in an observational retrospective review pIME, where respiratory caused pIME (13%) were less frequent compared to infectious (27%) and neurological (15%) caused pIME.[7] *Baltsezak et al.* reviewed 191 inflight air-to-ground calls (telemedical assistance calls) where 23 consultations (12.04%) were made for pediatric problems. [8]
Further, *Qureshi et al.* assessed IME over a 6 months period where half of the passengers with respiratory symptoms suffered from an acute asthma exacerbation, a third of them had forgotten their onboard medication. In their study, the exacerbation of pre-existing medical problems accounted for the majority of IMEs.[11]
Treating with IMEs entails aggravating circumstances including limited access to medical care, inappropriate emergency medical kit, limited space, increased onboard noise and vibrations and lack of availability of medically trained volunteers among air travelers.[12]

Focusing on respiratory IME we may struggle with several problems. Content of medical inflight kits are not standardized and differ between airlines. Most of them contain adult-sized ventilation devices such as bag mask, with risk for insufficient ventilation in pediatric age or harmful ventilation causing over ventilation, or even iatrogenic air leak syndrome. Not all of them contain bronchodilators and / or appropriate delivery mechanism (nebulizer machine or holding chamber) resulting in a non-efficient administration of the aerosol especially in young children.[13]

Inappropriate medical inflight kits are even more harmful considering that IMEs are more likely to occur on long distance flights, including Trans-Atlantic and Trans-Pacific flights, where emergency landing is impossible.[12]

To minimize the risk of (p)IME, evidence-based flight recommendations are essential but still sparsely available. Unfortunately, many guidelines are still based on physicians' experience and "experts" criteria, especially when dealing with the pediatric population.

Therefore, it is of utmost importance to perform clinical studies assessing patient´s flight safety to establish or reinforce the grade of evidence of (pediatric) flight recommendations and to give answer to physicians´ and parents' concerns: *"Under the current health conditions is it recommendable for my child to take a flight?"* or *"Is a this specific type of oxygen delivery system reliable to reverse flight induced hypoxia?"*.

With the current work the authors tried to give some evidence-based recommendations to improve flight risk assessment and to minimize (p)IME, in particular the safety for traveling on commercial flights of children after severe asthma exacerbation and the safety of portable oxygen concentrators as a source of oxygen in ex-premature infants.

1.2 PHYSICS OF AIR TRAVEL

1.2.1 Boyle´s law

Robert Boyle (1627–1691): pressure and volume of a gas (at constant temperature) are inversely related. For that reason a decrease in Pb leads to volume increase and vice versa.[14] *(Fig.1)*

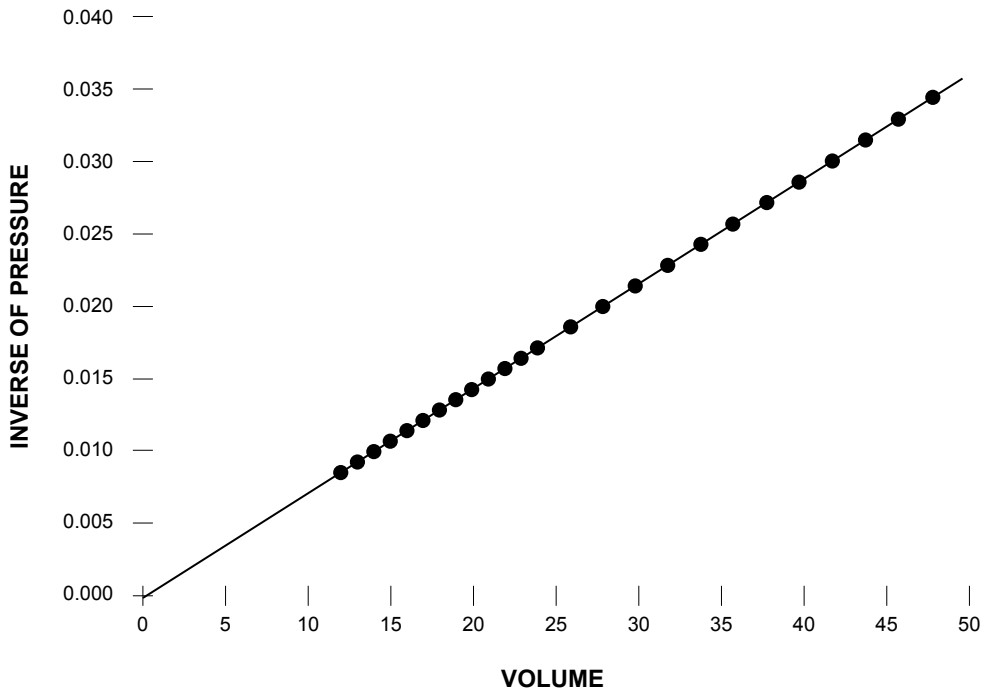


*Figure 1: Boyle´s law: pressure and volume of a gas are inversely related. Units on vertical axis are (inches of mercury)−1, and units on the horizontal axis are (cross-sectional area of the tube / 4) in cubic inches.*modified from West J.B. et al.*[15]

Inflight consequences derived from *Boyle´s law* is expansion of trapped air in human body cavities (cranial, thorax, abdomen, pelvis) causing air leak syndromes including pneumocephalus, pneumothorax, pneumomediastinum and pneumoperitoneum.

1.2.2 Dalton´s law

Total pressure in a gas mixture equals the sum of the partial gas pressures. *(Fig.2)*

P(total): P1+P2+P3+P4…

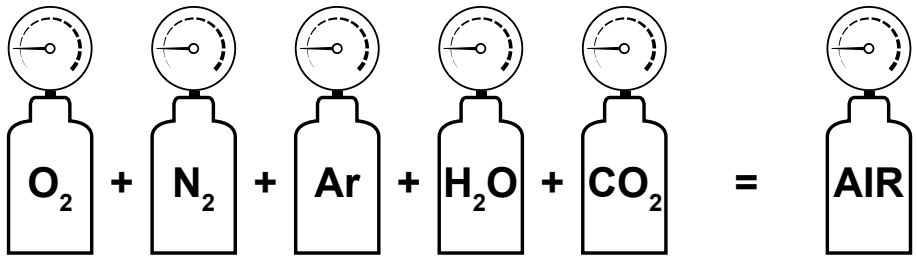


*Figure 2: Dalton´s law: Total pressure in a gas mixture equals the sum of partial gas pressures. *modified from Andrew Jarvis*[16]

1.2.3 Alveolar gas equation

$$PAO_2 = 0.21(Pb-47) - PACO_2/R$$

47 = water vapor pressure in mmHg at 37 °C; $PACO_2$ = alveolar partial pressure of carbon dioxide (around 40 mmHg with normal ventilation) ; R the respiratory exchange ratio (elimination of carbon dioxide/ uptake of oxygen) equals a 0.8 at rest); Pb: barometric pressure at sea level 760 mmHg

Chemical composition is constant for the entire troposphere but partial pressure reduces with ascending altitude. Troposphere: the lowest layer of Earth's atmosphere (10980 m at temperate latitudes, 7925 m at the poles and 18288 m a the equator).[17,18] *(Fig.3)*

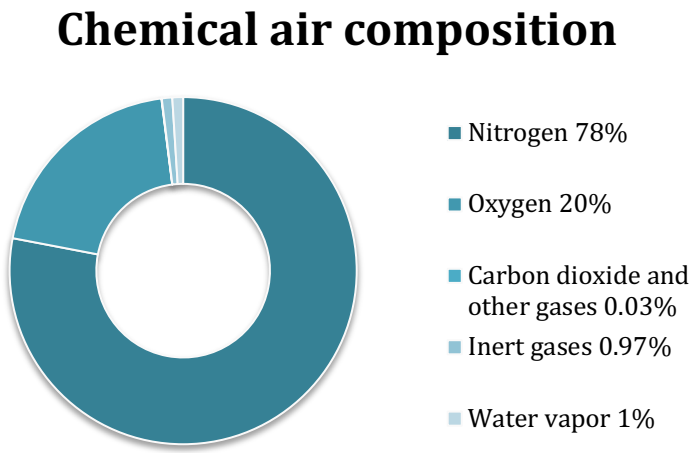


Figure 3: Chemical air composition

1.3 PHYSIOLOGY OF AIR TRAVEL

At sea level the human body is exposed to a barometric pressure (Pb) of 760 mmHg corresponding to partial oxygen tension (PO_2) of 150 mmHg and partial alveolar oxygen tension (PAO_2) 100 mmHg, comparable to fraction of inspired oxygen (FiO_2) of 0.21. With increasing altitude Pb decrease and is halved for every 5486 m dropping PO_2 levels. *(Tab.1)* In commercial aircrafts, at cruising altitude of 9000-13000 m, the Pb would decrease to 190 mmHg equivalent to PO_2 30 mmHg, PAO_2 0 mmHg and FiO_2 0.04. Therefore aircrafts have to be pressurized to a cabin altitude of 2438 m corresponding to Pb 564 mmHg, PO_2 109 mmHg, PAO_2 59 mmHg which is equivalent to breathing FiO_2 0.15.[17] *(Fig.4)* In 1988 *Cottrell et al.* measured inflight cabins altitudes on 204 aircrafts observing a median pressurized altitude of 1894 m (6214 ft) with a maximum of 2717 m (8915 ft) concluding that new generation aircrafts are able to fly at higher altitude resulting in a greater risk of altitude exposure of patients.[19] In 2013 *Hampson et al.* confirmed this theory observing a mean cabin altitude on 207 flights of 1933 m (6341 ft). Peak cabin altitude was significantly higher for long distance flights over 750 miles, a fact that physicians should take into account when determining supplemental oxygen during commercial air travel.[20]

Table 1: Altitude-related changes in barometric pressure, partial pressure of inspired oxygen and partial pressure of alveolar oxygen*

Height			**Pb (mmHg)**	**P_iO_2 (mmHg)**	**PAO_2 (mmHg)**
Meter	**Feet**				
0	0	Sea level	760	150	100
2000	6562		596	115	65
2438	8000	Cabin pressure	564	109	59
5000	16404		405	75	25
8848	29029	Everest summit	236	40	0
12000	39370	Cruising altitude	190	30	0

Pb: barometric pressure; P_iO_2: partial pressure of inspired oxygen; PAO_2: alveolar partial pressure of oxygen

* *modified from Israëls J et al.*[17]

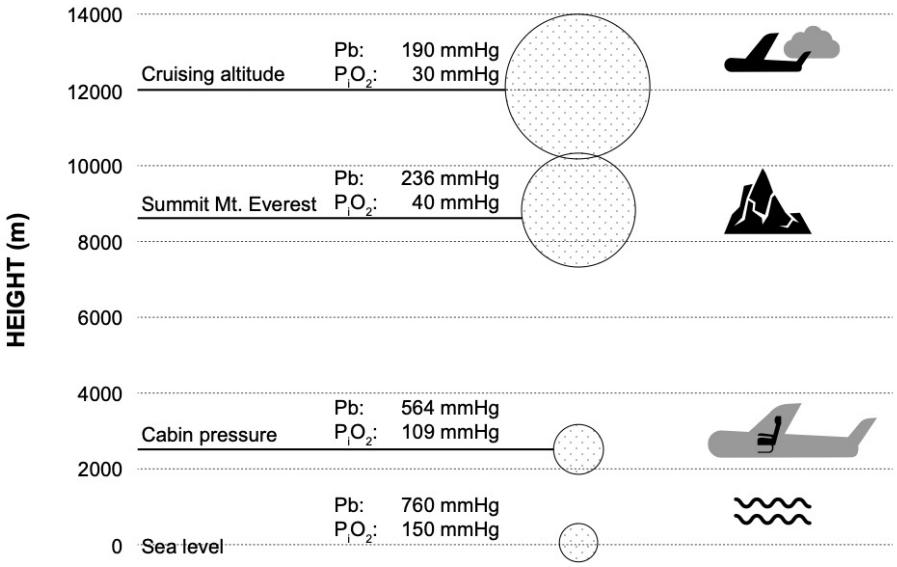


*Figure 4: Effect of height on barometric pressure, partial pressure of inspired O2 and expansion of trapped air. *modified from Israëls J. et al.*[17] *Pb, barometric pressure; P_iO_2, partial pressure of inspired oxygen*

1.3.1 Compensatory mechanisms to hypoxia

A decrease in PaO_2 stimulates the carotid chemoreceptors increasing minute volume (increased tidal volume and respiratory rate), cardiac output (HR x stroke volume) and pulmonary perfusion, accompanied by a vasoconstriction of the pulmonary artery and arterioles redistributing the pulmonary blood flow to the apical regions of the lung enhancing ventilation / perfusion mismatch leading to improved PAO_2. For older children or adults under normal health conditions this hypoxic state does not cause symptoms. Newborns and children < 1-year old show anatomical and physiological characteristics that imply limited hypoxic response. These characteristics are: presence of fetal hemoglobin (left shift of the oxygen dissociation curve), thoracic cage with greater compliance, increase in muscular pulmonary arterioles, a smaller airway diameter and decreased number of alveoli. All this implies a tendency to ventilation-perfusion mismatch, pulmonary vasoconstriction and bronchoconstriction under hypoxic state.[21,22] Therefore, carbon dioxide partial pressure (pCO_2) decreases leading to cerebral vasodilatation maintaining oxygen delivery to the brain. Another peculiarity is a paradoxical hypoxic response provoking inhibition of the respiratory center leading to hypoventilation and apnea which usually disappears after 6-8 weeks of life, although it may persist for a longer time in preterm newborns.[23] Flight duration of more than 6 hours is associated with an increased risk of hypoxic onboard events.[24]

1.3.2 Asthma & Hypoxemia

Mechanisms of hypoxemia include ventilation/perfusion (V/Q) mismatch, intrapulmonary right-to-left shunt, low inspired PO_2, alveolar diffusion impairment and hypoventilation. Concerning asthma, V/Q mismatch (normal V/Q: 0.8) is the main mechanism of gas exchange abnormality causing respiratory alkalosis. V/Q ratio is higher at the lung apex and lower at the lung base. Low V/Q ratio due to low PAO_2 levels produces hypoxemia and subsequently decreased PaO_2. By reducing perfusion to areas of the lungs with reduced ventilation (hypoxic pulmonary vasoconstriction), blood is diverted to the well-ventilated lung regions to maintain matching between ventilation and perfusion.[25,26] *(Fig.5)* After acute asthma exacerbation, despite preserved spirometric indices, improvement in V/Q mismatch occurs at the end of 4 weeks.[27] Spirometry indices (FEV1), which are measured at the mouth, reflect narrowing of large- and middle-sized bronchi whereas V/Q mismatch represent involvement of smaller peripheral airways.[28] In reverse, the V/Q ratio remains stable until FEV1 falls to 40% of the predicted FEV1 value. Below this level PaO_2 falls significantly. The presence of normal PaO_2 despite the clear evidence of gas exchange abnormality is due to the buffering action of high CO. PaO_2 may also remain normal despite V/Q mismatch and a high P(A-a) O_2 gradient.

In healthy lungs hypoventilation does not produce significant hypoxemia, however in presence of lung pathologies, hypoxemia might be severe causing atelectasis and widening of the P(A-a) O_2 gradient. Hypoxemia induced by hypoventilation, in absence of intrapulmonary shunts, is correctable with supplemental oxygen. *(Fig.6)*

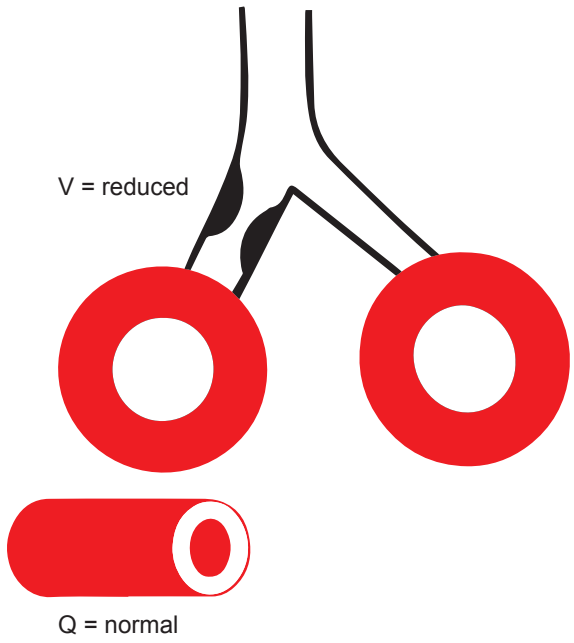


*Figure 5: Low V/Q ratio due to airway obstruction. No alteration in perfusion. *modified from Sarkar M. et al.*[25]

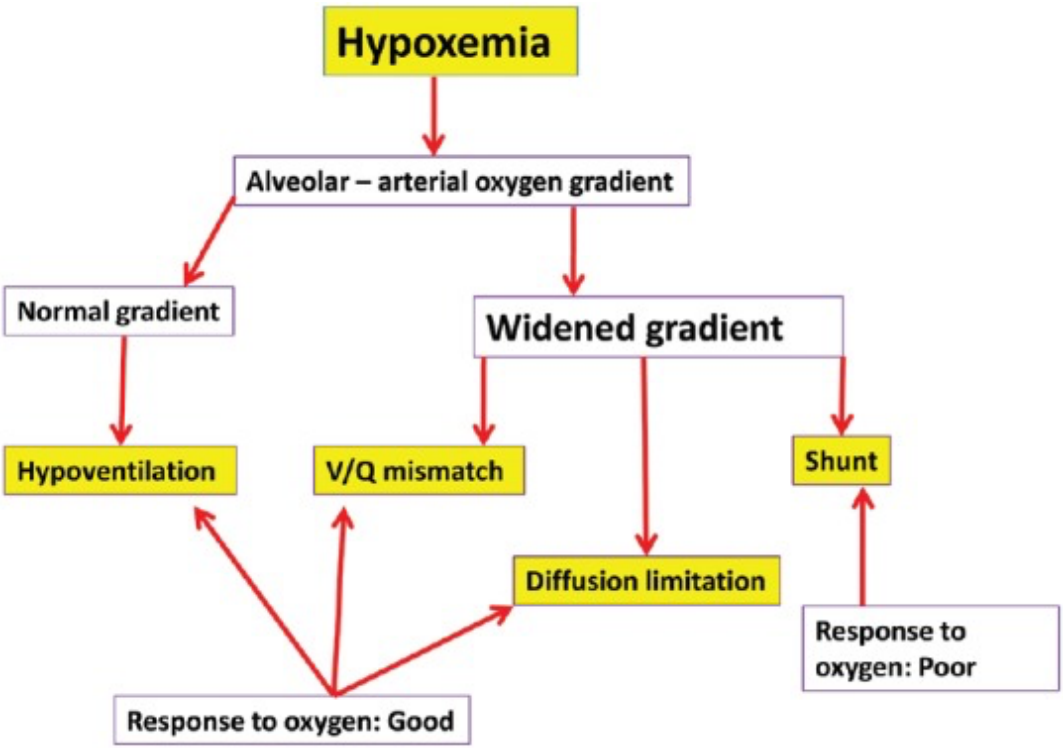


*Figure 6: Mechanisms of hypoxemia. Hypoventilation, V/Q mismatch and diffusion limitation show a good response to oxygen supply in contrast to intrapulmonary right-left shunt. *modified from Sarkar M. et al.*[25]

2 ASSESSMENT OF FITNESS TO FLY

2.1 WALKING TEST

Ability to walk 50 meters without respiratory distress. Poor scientific evidence and not applicable in newborns and infants.

2.2 PREDICTIVE EQUATIONS

Predictive PaO_2 equations derived from COPD patients. PaO_2 was measured in a hypobaric chamber before and during exposure to simulated altitude breathing FiO_2 0.15 from a reservoir bag. These equations seem to provide poor estimates of PaO_2 and the reliability in pediatric age remains unclear. Flight duration and cabin conditions are no simulated.[29,30]

2.3 HYPOXIC CHALLENGE TESTING

The simulation of hypobaric hypoxia is considered as the gold standard for fitness-to-fly testing requiring a hypobaric chamber, which is rarely available. Therefore whole-body plethysmograph chambers are used inducing normobaric hypoxia which is considered as a reliable alternative to titrate inflight oxygen requirements.[31] Patients are seated in an upright position in a hermetic chamber and baseline SaO_2, FiO_2 and HR are monitored. Afterwards nitrogen on a gas flow of 50 lpm is introduced decreasing FiO_2 from 0.21 to 0.15 simulating the inflight conditions of a pressurized aircraft cabin. Patients are breathing this hypoxic gas mixture for 20 minutes. FiO_2, SaO_2 and HR are continuously monitored. In case of SaO_2 drop ≤ 85 % (or < 90% in patients > 1 year), oxygen is administered and oxygen requirements are titrated.[32] *(Tab.2)* If no plethysmograph is available, breathing through a Douglas bag or inhalation of a prefabricated hypoxic gas mixture (FiO_2 0.15) is a valid alternative method but oxygen titration is technically more complicated and therefore is less reliable. Another simple alternative is the use of a *VenturiMask®* on FiO_2 0.35 and adding nitrogen as driving gas achieving a hypoxic gas mixture of about 0.15.[33]

BTS recommendations for inflight hypoxic risk assessment are listed in table 2. *(Tab.2)*

Table 2: Recommendations BTS guidelines inflight hypoxic risk assessment

Pre-flight assessment in pediatric age[2,17]		
Age	**Recommendation**	**Threshold for oxygen supply (1-2 lpm):**
Full-term (> 37 wks)	Delay flight 1 week after birth	n/a
Preterm newborn (< 37 wks) non-BPD	> 3 months of corrected gestational age and well	
Preterm newborn (< 37 wks) + BPD	HCT	n/a
< 1 year and history of neonatal chronic respiratory disease	HCT	SaO_2 < 85%
Chronic lung disease (e.g. cystic fibrosis)	Spirometry. If FEV1 < 50% or severe respiratory disease, HCT is recommended	SaO_2 < 90%
Infants with oxygen requirements at sea level	Double oxygen flow rate. Refrain from flight if > 4 lpm.	n/a
Infants with long-term oxygen requirements in the last 6 months	HCT	n/a
After acute asthma exacerbation	Lack of evidence-based recommendations	
Air leak syndrome (ALS)	Check resolution before flight. Delay flight 7 days in case of spontaneous ALS and 14 days if traumatic ALS	n/a
Long-term ventilation for pulmonary disease	Lack of evidence-based recommendations	
Acute respiratory infection	Refrain from flight until recovery	
Anemia	Hemoglobin level > 8.5 g/dl	
Cyanotic heart disease	Lack of evidence-based recommendations	
Pulmonary hypertension	Lack of evidence-based recommendations	

3 Logistics of oxygen supply

Logistical details for onboard oxygen supply are listed in table 3. *(Tab.3)*

Table 3: Logistics of onboard oxygen / ventilation supply

Logistics of oxygen supply		
Liquid oxygen	Prohibited	
Small oxygen cylinders	Pre-flight agreement with airline	
Airline oxygen supply	Pre-flight reservation	
Portable oxygen concentrator (POC)	Approved by FAA[34]	*The European Lung Foundation (ELF)* provides information about POC renting from airline companies[35]
Ventilator support	Specialist advice is required. Medical escort in intubated patients. Manual bag ventilation during take-off and landing.	

4 POC operation

POCs compressor forces room air through a cylinder which contains a molecular sieve that contains silicate granules (zeolite) where nitrogen is absorbed, oxygen concentrated and released to a pressure-equalizing reservoir. Some models provide a heat-exchanger that decreases the compressed air temperature improving nitrogen absorption. *(Fig.7)* Therefore, gas pressure decreases in the first cylinder, the valve closes and nitrogen released into ambient air. POCs have the capacity to concentrate oxygen up to FiO_2 0.90-0.95 at sea level, which decreases in high altitude. Oxygen is delivered through nasal cannulas to the patient via continuous-flow (cPOC) or pulsed-flow (pPOC) delivery. A small amount of oxygen is retained in the pressure-reduced sieves enhancing the washout of the remaining part of nitrogen. Afterwards the next oxygen concentration cycle begins which is reversed every 5-10 seconds so both molecular sieve bed are alternately adsorbing and purging.[36,37]

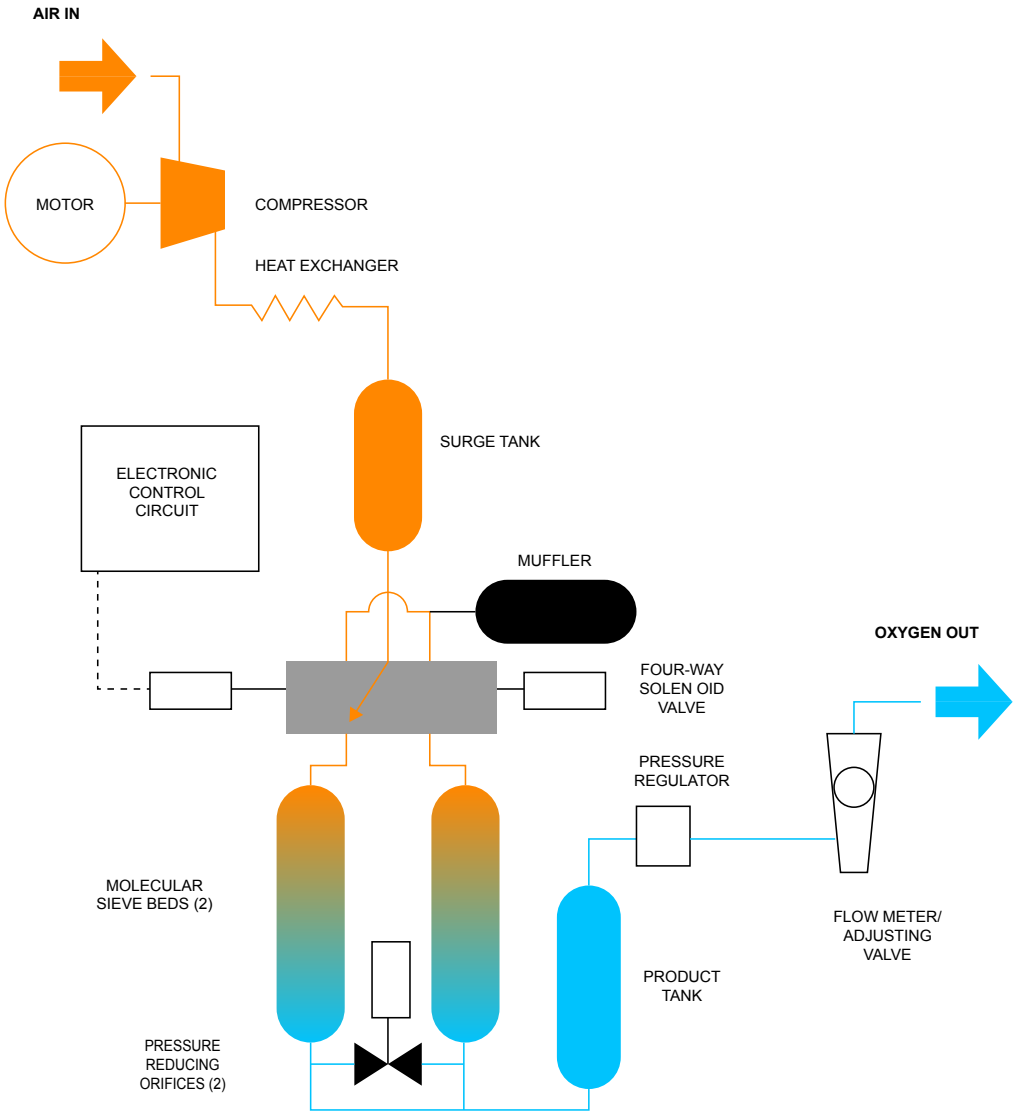


*Figure 7: Conventional Two-Bed Oxygen Concentrator. *modified from MEDI-AID SYSTEMS*[36]

5 JUSTIFICATION OF RESEARCH

The number of air travelers is steadily increasing over recent years implying an increasing number of passengers in infancy and early childhood. In future physicians will be more often challenged to give evidence-based flight recommendations, especially for patients suffering from chronic respiratory, cardiac, neuromuscular or hematological diseases.[1,2] Unfortunately, many guidelines on inflight safety are based on studies in adults or with a low grade of evidence, especially in the pediatric population. For this particular reason pediatric flight safety should be considered as a public health issue requiring intensified research in this specific field. Therefore, we decided to design two flight risk assessment trials in children to give answer to two specific questions that have arisen in the past few years. *"At what time is it safe for my child to travel by plane after a severe asthma attack?"* and *"Is it safe for my child to use Portable Oxygen Concentrators during the flight?".* The Pediatric Department of University Hospital Son Espases performs HCT since 2006. This expertise led to national and international publications thin this specific field.[21,38]

6 STUDY POPULATION

Pediatric age range includes from birth to 14 years of age, and in some countries up to 18 years. Respiratory physiology is changing constantly during this growth period. As described previously Pb and PaO_2 decrease with increasing altitude exposing air travelers to hypoxia despite aircraft cabin pressurization. Under normal health conditions this hypoxic state does not cause symptoms whereas patients suffering from respiratory, cardiologic or hematologic diseases may develop respiratory or neurological symptoms. Newborns < 1 year of age and ex-preterm are particularly more vulnerable to these conditions and may show impaired hypoxic response. Therefore, we focused research on this study population.

MATERIAL & METHODS

7 MATERIAL & METHODS

This doctoral thesis includes 2 Research Projects related to HCT.

Research Project 1: Assessing hypoxia risk during air travel after a severe asthma exacerbation

Research Project 2: Use of Portable Oxygen Concentrators (POCs) to correct HCT induced hypoxia

HCT performance at the Pediatric Pulmonology Function Testing Laboratory at University Hospital Son Espases, Balearic Islands, Spain.

8 Research Project 1.

Working title: Assessing hypoxia risk during air travel after severe asthma exacerbation

8.1 INTRODUCTION

Asthma is reported to be the most common potentially life-threating condition encountered on flights. Different guidelines assessing fitness-to-fly have been published but there are no specific recommendations regarding hypoxia risk or for how long the flight should be postponed after hospitalization due to asthma exacerbation with oxygen requirements.

8.2 HYPOTHESIS

H_0: Pediatric patients recovering from an acute asthmatic exacerbation, pass HCT in the first 48 hours after removing oxygen therapy.

H_1: Pediatric patients recovering from an acute asthmatic exacerbation, do NOT pass HCT in the first 48 hours after removing oxygen therapy.

8.3 AIMS

The main objective is to determine hypoxia risk during air travel after hospitalization for severe asthmatic exacerbation performing HCT in pediatric patients. A secondary objective is to determine the risk of hypoxia during HCT in relation to lung function and other conditions.

8.4 Material & Methods

8.4.1 Study design

Prospective observational study. Ethics approval was granted *(IB 1867/12).*

8.4.2 Inclusion criteria

Patients (2-15 years) hospitalized due to severe asthma exacerbation with oxygen dependence (baseline SaO_2 < 92%) who were planning a flight after hospital discharge.

8.4.3 Exclusion criteria

Respiratory (except asthma), cardiovascular, neurological or hematological diseases.

8.4.4 Procedure

Epidemiological data, clinical variables, duration of hospitalization and oxygen therapy data are collected. After completing 24 hours without oxygen requirements and baseline SaO_2 ≥ 92%, including feeding and sleeping periods, a spirometry following *ATS/ERS guidelines* and HCT was performed as described previously.[39] If SaO_2 drop to < 90% we titrated oxygen supply until hypoxia state recovery (SaO_2 > 92%). Patients who remained with a SaO_2 > 90% at FiO_2 0.15 for 20 minutes were considered "no inflight hypoxia risk". Those who failed the test were requested to repeat HCT after 24 hours.

- ✧ Plethysmograph *(MasterScreen Body®,Erich Jaeger)*
- ✧ Pulse oximeter *(Masimo SET-Radical-7-Electron®)*

8.5 Statistical analysis

SPSS 12.0. (IBM Corp.; Armonk,NY) For hypothesis contrast and correlation analysis between lung function parameters and HCT outcomes the *Mann-Whitney Test* was performed.

9 Research project 2.

Working title: Use of Portable Oxygen Concentrators (POCs) to correct HCT induced hypoxia

9.1 INTRODUCTION

In case of inflight hypoxia, oxygen supply is required. Recently the *FAA* approved the use of POCs for onboard oxygen administration. These devices are divided into two different types: continuous-flow (cPOC) and pulsed-flow (pPOC). Despite being used in everyday life, there are few studies proving their safety in an environment of simulated hypoxia in adults and no studies that demonstrate their effectiveness in the pediatric population. Despite the fact that POCs are widely used in pediatric units including at the University Hospital Son Espases, the parameters for minimum patient age or weight, even at sea level, remain unknown due to a lack of studies. Moreover, pPOCs are designed for adults and not recommended in pediatric age.

9.2 HYPOTHESIS

H_0: Both tested POCs are effective to revert HCT induced hypoxia in pediatric patients suffering from respiratory disease.

H_1: Both tested POCs are NOT effective to revert HCT induced hypoxia in pediatric patients suffering from respiratory disease.

9.3 AIMS

Main objective: to assess the effectiveness of POCs to revert HCT induced hypoxia (at simulated altitude conditions) in pediatric patients. Secondary objective: compare cPOC and pPOC concerning patient age, weight and previous pathology.

9.4 MATERIAL & METHODS

9.4.1 Study design

Randomised controlled crossover trial. Ethics approval was granted *(IB 3155/16).*

9.4.2 Inclusion criteria

- Infants < 1 year with neonatal respiratory disease
- Patients with oxygen therapy (in the last 6 months)
- Patients with chronic respiratory disease (e.g. cystic fibrosis, obstructive or restrictive lung disease) with FEV 1 or FVC < 50%

9.4.3 Exclusion criteria

- Acute respiratory infection

9.4.4 Procedure

HCT is performed as previously described. FiO_2, SaO_2 and HR are continuously monitored for 20 minutes. In case of SaO_2 drop ≤ 85%, oxygen is administered by cPOC or pPOC according to randomization (crossover design) until the hypoxic state was reverted. In case of SaO_2 drop ≤ 85%, oxygen is administered by POC through nasal cannula until baseline SaO_2 is achieved. In case of refractory hypoxia, HCT is interrupted, returning to ambient conditions (FiO_2 0.21) and liquid oxygen administered. The patient is deemed NOT fit to fly. For patients who show a positive POC hypoxic reversal, HCT is repeated after 24 hours under the same conditions. In cases of hypoxia, oxygen is administered by the pending POC to test. *(Fig.8)*

i

- ✧ POC continuous-flow mode (cPOC): *SeQal Eclipse 3® (SeQual,Ball Ground,GA)* on at flow rate 2 lpm
- ✧ POC pulsed-flow mode (pPOC): *InogenOne G3® (Inogen,Goleta,CA)* on setting 2 (flow 420 ml/min, 16 ml/bolus at 25 rpm)

- ✧ Plethysmograph *(MasterScreen Body®,Erich Jaeger)*
- ✧ Pulse oximeter *(Masimo SET-Radical-7-Electron®)*

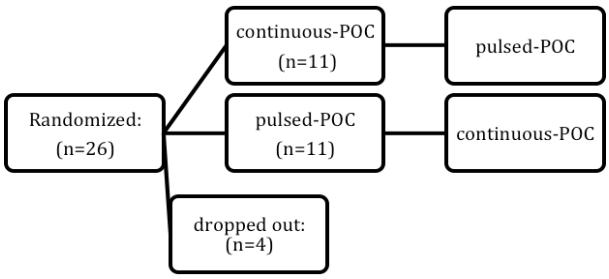


Figure 8: Simplified flow chart patient recruitment

9.5 Statistical analysis

Variables were compared among techniques using *Student's T-test* for paired samples, or *Wilcoxon's test* (non-parametric, based on rank transformation). The level of significance was set at p values < 0.05. *SPSS 23.0 (IBM Corp.; Armonk,NY)* was used for statistical analyses.

10 ETHICAL ASPECTS

The provisions of *LAW 14/2007*, of July 3, of biomedical research were followed. Ethical principles were followed for medical research in humans from the *Declaration of Helsinki*. Informed consent was given to all tutors and assent to those over 12 years of age. Both research protocols were evaluated and approved by the Ethics Committee of the Balearic Islands with registration numbers *IB 1867/12* and *IB 3155/16.*

11 SCHEDULE

Research Project 1.

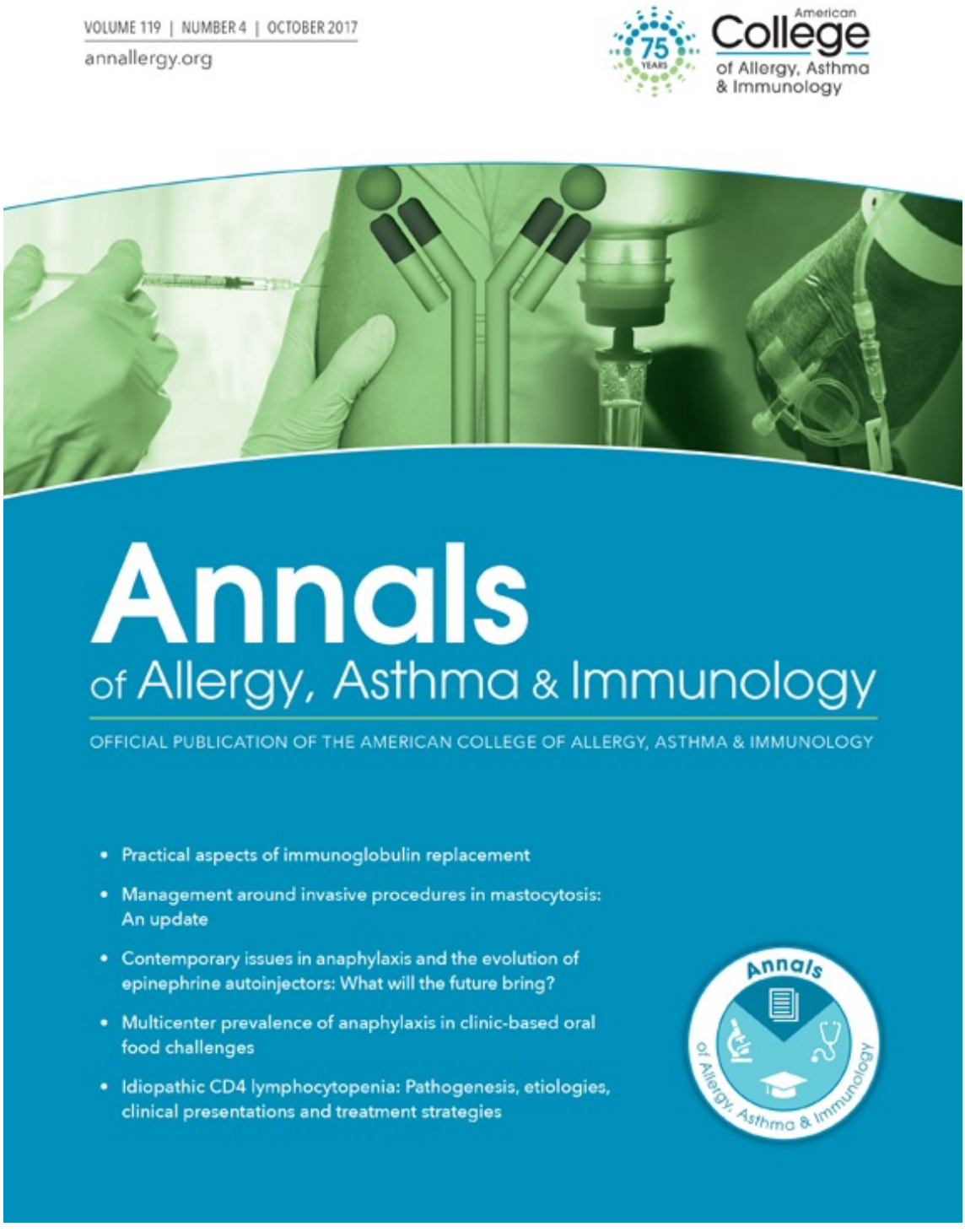
(1) Presentation and Ethic Committee approval (12/2014)
(2) Patient Recruitment (01/2015-12/2016)
(3) Data analysis (01/2017)
(4) Publication (10/2017)

Research Project 2.

(1) Presentation and Ethic Committee approval (02/2016)
(2) Patient Recruitment (02/2016-01/2019)
(3) Data analysis (01/2019)
(4) Publication (03/2020)

PUBLISHED ARTICLES

12 PUBLISHED ARTICLES



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Assessing hypoxia risk during air travel after a severe asthma exacerbation in children

Decreased atmospheric cabin pressure in commercial aircrafts (cruising altitude 9,000–13,000 m), requiring cabin pressurization from 1,530 to 2,440 m, is equivalent to breathing a fraction of inspired oxygen (FiO_2) of 15.1% at sea level.

These conditions can cause severe hypoxia in patients with chronic respiratory disease. The normobaric hypoxic challenge test (HCT) is the recommended method to estimate the risk of in-flight hypoxia in patients with respiratory disease, allowing symptom observation and titration of oxygen (O_2) requirements.[1] Asthma is reported to be the most common potentially life-threating condition encountered during flight.[2] Different guidelines assessing fitness to fly have been published, but there are no specific recommendations for hypoxia risk or for how long the flight should be postponed after hospitalization for asthma exacerbation with O_2 requirements.[1,3,4]

Our main objective was to determine hypoxia risk during air travel after hospitalization for severe asthmatic exacerbation by performing the HCT in children. A secondary objective was to determine the risk of hypoxia during the HCT in relation to lung function and other conditions.

This prospective study was performed at a pediatric pulmonology function testing laboratory in a tertiary care hospital. Ethics approval was granted (IBNo1867/12 PI). All parents signed informed consent.

We included patients (2–15 years old) hospitalized for severe asthma exacerbation with O_2 dependence (baseline O_2 saturation [SpO_2] $< 92\%$) who were planning a flight after discharge. Exclusion criteria were respiratory (except asthma), cardiovascular, neurologic, or hematologic diseases. Epidemiologic data, clinical variables, duration of hospitalization, and use of O_2 therapy were collected. After completing 24 hours without a need for O_2, including feeding and sleeping periods (baseline $SpO_2 \geq 92\%$), spirometry was carried out according to American Thoracic Society and European Respiratory Society guidelines. Then, the HCT was performed according to the recommended method[1] by introducing nitrogen (50 L/min) in a sealed body plethysmograph (Jaeger MasterScreen Body, Becton-Dickinson, Franklin Lakes, New Jersey) that lowered FiO_2 from 21% to 15%, simulating hypoxia during air travel. SpO_2 and heart rate were monitored by continuous pulse oximetry. If SpO_2 decreased to lower than 90%, we titrated O_2 until hypoxia was resolved ($SpO_2 > 92\%$). Patients who remained with an SpO_2 higher than 90% at an FiO_2 of 15% for 20 minutes were considered a "no in-flight hypoxia risk." Those who did not were requested to repeat the HCT after 24 hours.

For statistical analysis we used SPSS 12.0 (SPSS, Inc, Chicago, Illinois). To test the hypothesis and analyze the correlation between lung function parameters and HCT outcomes, we performed the Mann-Whitney test.

Fifty-one children (27 boys, mean age 6.5 years, range 2.5–12.2) were recruited from January 2014 through December 2016. Demographic and clinical data such as spirometry and HCT results are listed in Table 1. Forty-six of 51 children (90%) passed the HCT after 24 hours without O_2 therapy and were considered a no in-flight hypoxia risk. Of those 5 of 51 (10%) who did not pass, the HCT was repeated after 48 hours without O_2 and all (100%) passed the test. Mean decrease in SpO_2 while performing the HCT was 4.5%. Patients who did not pass the HCT within the first 24 hours showed lower mean forced expiratory volume in 1 second (FEV_1) compared with the group who passed the HCT (FEV_1 69% vs 89%, $P = .038$). No differences were found in SpO_2 before the HCT, days of hospitalization, required O_2, and maximum FiO_2. No significant side effects while performing the HCT were observed.

Because of socioeconomic changes, the number of air travel passengers has been increasing steadily in recent years. During air travel PaO_2 can decrease to 60 mm Hg in travelers without pulmonary disease, causing mild hypoxia, but the shape of the oxygen-hemoglobin dissociation curve usually prevents SpO_2 decreases lower than 92%. In patients with respiratory diseases, SpO_2 decreases are more severe. Sometimes air travel after hospitalization for asthmatic exacerbation is unavoidable. Unfortunately, there is a lack of recommendations for how long air travel should be delayed after hospital discharge.

Most guidelines consider pulse oximetry or arterial gasometry values when selecting patients with hypoxia risk during flights. In fact, patients with PaO_2 higher than 70 mm Hg or SpO_2 higher than 95% are considered fit to fly in most cases. Nevertheless, in recent years, different studies have shown that the "fit-to-fly criteria" based on basal PaO_2 are insufficient.[3,5] Equations might be used to predict in-flight PaO_2; however, these equations are derived from patients with chronic obstructive pulmonary disease, interstitial lung disease, and cystic fibrosis. Their precision remains unclear in patients with asthma but improves in those with other lung diseases after introducing FEV_1 or ratio of FEV_1 to forced vital capacity values.[6,7] Particularly in adult patients with severe asthma, baseline O_2 saturation appears to be a poor predictor for the need for in-flight O_2.[8]

Performance of the HCT offers several advantages over equations. It is an individual and more accurate evaluation and allows for an observation of clinical signs of hypoxia. Nevertheless, the HCT has a number of limitations because cabin pressure and density are not reproduced.

This is the first study assessing in-flight hypoxia risk in children with asthma who were hospitalized for asthmatic exacerbation and required O_2. Although the reliability of the HCT is under discussion, it still is considered the most appropriate test for preflight evaluation.[1,9] Despite including patients with high O_2 requirements during hospitalization (FiO_2 up to 100% and 14 days of admission), no increased risk of hypoxia while

Disclosures: Authors have nothing to disclose.

Table 1
HTC Results in Asthmatic Patients

	Total	Patients passed HTC in first 24 h	Patients failed HTC in first 24 h	*P*
n	51	46	5	
Age, y (mean ± SD)	6.5 (3–12,2)	6.4 ± 2.8	8 ± 1.3	NS
FEV_1 pre-HCT (mean ± SD)	85% (42–120%)	88.1 ± 0.16	68.8 ± 0.18	.038
FiO_2 max (mean ± SD)	0.35 (0.28–1)	0.43 ± 0.18	0.4 ± 0.16	NS
SpO_2 pre-HCT (mean ± SD)	96% (92–99%)	96 ± 1.8	94 ± 1.5	NS
Minimum O_2 saturation during test (%)		92	88	NS
Mean O_2 saturation drop (%)		4.2	6	NS
Days of admission (mean ± SD)	4.9 (3–14)	4.8 ± 2.2	5 ± 1	NS

Abbreviations: FEV_1, forced expiratory volume in 1 second; FiO_2 max, maximum fraction of inspired oxygen during hospitalization; HCT, hypoxic challenge test; NS, not significant.

performing the HCT was observed, a fact that makes our results more consistent.

According to our data, in children hospitalized for asthma exacerbation without O_2 therapy for 48 hours, no increased in-flight hypoxia risk was detected and performance of the HCT was not necessary.

In our study, the group who did not pass the HCT in the first 24 hours after O_2 therapy showed lower pretest FEV_1 values, and although this it does not seem to be a sufficiently reliable indicator, an FEV_1 lower than 70% has to be taken into account.

The main limitation of our study is that the HCT was not performed in a hypobaric chamber, and although the results for hypoxia were similar to those of previous studies, symptoms from lower cabin pressure can appear. Another limitation is that PaO_2 values are not registered. This painful test is not used habitually in children because of ethical concerns.

In conclusion, pediatric patients with acute respiratory failure from asthmatic exacerbation requiring hospitalization are passing the HCT in the first 48 hours after removing O_2 therapy. These results suggest a low risk of hypoxia during air travel after this period. Although other concerns such as humidity, pressure and temperature variability have to be considered, this study could provide information as to how soon after severe asthmatic exacerbation it is safe to fly.

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Disseminated *Mycobacterium avium intracellulare* leading to protein-losing enteropathy in an elderly man with idiopathic CD4 lymphocytopenia

Idiopathic CD4 lymphocytopenia (ICL) is a clinical diagnosis in which $CD4^+$ T lymphocytes constitute fewer than 300 cells/μL or fewer than 20% of total T cells without evidence of human immunodeficiency virus (HIV) or any defined immunodeficiency or therapy associated with decreased levels of $CD4^+$ T cells.[1] Mycobacterium is one of the most common opportunistic infections in ICL. We report on a unique case of a 64-year-old man with ICL who developed protein-losing enteropathy (PLE) secondary to disseminated *Mycobacterium avium intracellulare* (MAI) infection that resolved with successful treatment of the mycobacterium infection.

A 64-year-old man presented with a 2-year history of persistent skin nodules that were positive for *Aureobasidium* species, *Alternaria* species, and *Hortaea werneckii*. He required multiple treatment courses with itraconazole, flucytosine, and voriconazole to clear the nodules. Because of recurrent cutaneous fungal infections, an immunodeficiency was suspected. Workup demonstrated persistent severe lymphopenia (151 cells/μL) coupled with low immunoglobulin (Ig) levels (IgM <13 mg/dL, IgG 609 mg/dL, IgA 67 mg/dL, CD4 level 7 cells/μL) and lack of mitogen response. Polymerase chain reaction results for HIV-1 and -2 were negative. Adenosine deaminase levels were normal. Antibacterial treatment with trimethoprim plus sulfamethoxazole was started. In the absence of secondary immunodeficiency, ICL was diagnosed.

During his hospital admission for symptomatic hypoglycemia, the patient reported a 20-pound weight loss during the past 3 to 4 months. Chest radiograph showed bilateral noncalcified pulmonary nodules that were confirmed on chest computed tomogram. Bone marrow aspiration failed to demonstrate malignancy. However, a positron emission tomogram showed hypermetabolic bilateral lung nodes and mesenteric lymphadenopathy. Further workup demonstrated a low protein level, a normal α_1-antitrypsin level in stool, hypogammaglobulinemia, and lack of response to pneumococcal immunization. Therefore, intravenous immunoglobulin replacement was started. Two months later, the patient complained of mild abdominal discomfort and fatigue, with no fever or cough. On physical examination, the patient was found to have an ashy skin color, ascites, muscle wasting, healed skin nodules, and anasarca. At this time, laboratory tests showed microcytic anemia (hemoglobin 8.6 g/dL, mean corpuscular volume 63.1 fL, serum iron 16 μg/dL, total iron binding capacity 250 μg/dL, ferritin 34.8 ng/mL,

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REGULAR ARTICLE

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

Assessment of portable oxygen concentrators in infants undergoing hypoxic challenge testing. A randomised controlled crossover trial

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Abstract

Aim: Due to reduced PaO_2, aircrafts at cruising altitudes are pressurised to a cabin altitude of 2438 m, equivalent to breathing FiO_2 0.15. Portable oxygen concentrators (POCs) are approved for onboard oxygen supply with lack of evidence, especially in infants. We assessed POCs (continuous-flow cPOC vs. pulsed-flow pPOC) under simulated altitude conditions performing Hypoxic Challenge Testing (HCT).

Methods: In a randomised controlled crossover trial, we included patients <1 year born prematurely. In incidents of hypoxia (SpO_2 ≤ 85%), oxygen was administered through POC. In patients with a positive hypoxia reversal, HCT was repeated 24 hours later. If hypoxia occurred during the second testing, oxygen was given using the alternative POC.

Results: We randomised 26 patients; 22 patients received allocated intervention (4 dropped out). Mean gestational age 30.4 weeks, mean corrected age 38.2 weeks. Both POCs achieved immediate hypoxia reversal in all cases (SpO_2 cPOC/pPOC 98%/99.4% (95%CI −2.91, 0.01)) without any adverse events. No significant difference was observed in patients with BPD.

Conclusion: Both POCs generated sufficient oxygen to reverse HCT induced hypoxia. Although pPOCs are not recommended in paediatric age, our data suggest their effectiveness even in neonates without any associated adverse events. Future research on pPOCs safety is required to establish recommendations for their use.

KEYWORDS

hypoxia altitude simulation test, hypoxic challenge testing, infants, neonates, portable oxygen concentrators

1 | INTRODUCTION

Due to reduced barometric pressure and PaO_2, aircrafts at cruising altitude (9000-13000 m) are pressurised to a cabin altitude of 2438 m which is equivalent to breathing FiO_2 0.15. Under normal health conditions, this hypoxic state does not cause symptoms due to increased respiratory minute volume and cardiac output, which maximises alveolar oxygen tension. Patients with compromised health conditions may show impaired hypoxic response.[1]

RCT REGISTRATION: ClinicalTrials.gov registration number: (NCT03976986)

According to a forecast by the *International Air Transport Association* the number of people travelling on commercial aircraft is predicted to rise to 8.2 billion passengers in 2037. Therefore evidence-based flight recommendations will gain in future importance, especially for patients suffering from chronic diseases.[2] Hypoxic Challenge Testing (HCT) is the recommended method for inflight hypoxia risk assessment where nitrogen is introduced in a plethysmograph reducing FiO_2 to 0.15. Oxygen supply is recommended if PaO_2 drops < 50-55 mm Hg (in adults) or SpO_2 ≤ 85% (in infants) where non-invasive pulse oximetry is the recommended method for hypoxia assessment.[2-4] Onboard oxygen administration remains controversial. The *Federal Aviation Administration* approved portable oxygen concentrators (POCs) for onboard oxygen supply.[2,5,6] However, evidence on POC use in adults is poor and there are currently no studies on their use in paediatric and neonatal ages. The use of pulsed-flow devices remains especially unclear for neonates, infants and small children due to shallow breathing patterns and therefore the *British Thoracic Society* and *American Thoracic Society* do not recommend their use.[7,8] The aim of our study was to test POCs under simulated altitude conditions performing HCT in paediatric age subjects. Primary objective: Assessing POCs effectiveness for hypoxia reversal (by means of pulse oximetry values) performing normobaric HCT according to *BTS guidelines*.[2] Secondary objective: To assess differences between continuous-flow portable oxygen concentrator (cPOC) and pulsed-flow portable oxygen concentrator (pPOC) concerning hypoxia reversal capacity.

Key notes

- Hypoxic Challenge Testing (HCT) is the recommended method for inflight hypoxia risk assessment.
- Portable oxygen concentrators (POCs) are approved for onboard oxygen supply but there is a lack of evidence to support their use especially in infants.
- In our randomised controlled crossover trial both tested POCs (continuous-flow/ pulsed-flow) generated sufficient oxygen to reverse HCT induced hypoxia.

2 | MATERIAL AND METHODS

We conducted a randomised controlled crossover trial (pilot study) including 26 patients under 1 year of age born prematurely who underwent HCT. The study was performed at the Paediatric Pulmonary Function Testing Laboratory, Paediatric Respiratory Unit, University Hospital Son Espases. The results were related to the clinical-epidemiological data collected in the patient's medical history. As dependent variables, we collected SpO_2 and heart rate before and during HCT, as independent variables type of POC, age (months) and weight (kg). Inclusion criteria were baseline SpO_2 of >94% in infants <1 year with neonatal respiratory disease or required oxygen supply in the last 6 months. Exclusion criterion was acute respiratory infection. Tested POCs: *SeQal Eclipse 3*® (*SeQual, Ball Ground, GA*) on continuous-flow mode (cPOC) at flow rate 2 L/min and *InogenOne G3*® (*Inogen, Goleta, CA*) on pulsed-flow mode (pPOC) setting 2 (flow rate 420 mL/min, 16.8 ± 3 mL per bolus at 25 rpm). As a pulsed device, the pPOC has a 'Breath Detection Alert Mode'. This backup mode alerts the user with audible and visual signals in case of apnoea or inability to detect patient's inspiration (if more than 60 seconds), and the 'auto pulse mode' (backup mode) is initiated until the next inspiration is detected. A software-generated random list was created using a 2 × 2 Latin square with cPOC and pPOC assignation codes. After patient recruitment, the corresponding order number was checked in strict consecutive order. Patients were allocated to two study groups (cPOC/pPOC) according to the random list. Before HCT performance the mother was introduced to POC function and the correct oxygen cannula (*neonatal, Klinik Health*®) positioning in case of hypoxia. The patient, seated on the mother´s lap, and the POC were positioned inside a sealed plethysmograph (*MasterScreen Body*®, *Erich Jaeger*) without flexing the neck. No feeding was done during testing. SpO_2 and pulse rate were measured with a *Masimo SET-Radical-7-Electron*® *pulse oximeter.* Nitrogen was introduced (flow rate of 50 L/min), reducing FiO_2 to 0.15 (*MiniOx3000*®, *Medical Products*). FiO_2, SpO_2 and heart rate were continuously observed for 20 minutes. In case of SpO_2 drop ≤ 85%, the mother positioned the oxygen cannula as indicated previously without opening the door of the plethysmograph and oxygen supply was given through POC. In case of refractory hypoxia, HCT was stopped and the patient was deemed not fit to fly. For patients who showed a positive POC hypoxic reversal, HCT was repeated 24 hours later. If any hypoxic events occurred during the second testing, oxygen was given using the alternative POC which was yet to be tested. All parents gave informed consent, ethics approval was granted by the Institutional Ethics Committee (*IB 3155/16*) and the trial was registered: *clinicaltrials.gov* (*NCT03976986*).

2.1 | Statistical analyses

The sample size was calculated for a phase 2 study (pilot study) whose main objective is to determine with accuracy the expected differences between the methods of oxygen administration (continuous vs pulsed flow). For this purpose, the sample size was determined based on the estimation of these differences according to the methodology proposed by Cocks et al (*Cocks K, Torgerson DJ, Sample size calculations for pilot randomised trials: a confidence interval approach, J Clin Epidemiol.; 66:197-201.*) Data are expressed using mean ± SD, ±95%CI. Variables were compared among techniques using Student's *t* test for paired samples. Level of significance: *P*-values < .05. SPSS 23.0 (*IBM Corp.*) was used for statistical analyses.

3 | RESULTS

We performed HCT in 26 patients (02/2016-02/2019) born prematurely with a mean gestational age of 30.4 weeks (range: 25-36) including 15 patients without bronchopulmonary dysplasia (BPD), 6 patients with BPD and 1 patient with BPD and subglottic stenosis. Four patients dropped out after randomisation due to incorrect study protocol application (Figure 1). HCT was performed at a mean corrected age of 38.2 weeks. Both tested POCs achieved immediate hypoxia reversion in all cases without any adverse events. Mean maximum SpO_2 achieved was 98% in the cPOC and 99.4% in the pPOC arm (p 0.051). No significant difference was observed between preterm patients with or without BPD concerning POC response. Demographic and clinical data are listed in Table 1 and comparison analysis cPOC/pPOC in Table 2.

4 | DISCUSSION

Despite the use onboard POCs being widely practiced, there is lack of evidence on their effectiveness and safety during air travel, especially for paediatric and neonatal patients. POC use is approved by the *FAA* and the *European Lung Foundation* (*ELF*) provides information about POC rental from airline companies.[6,9] Parents who are travelling with an oxygen-dependent infant may encounter several logistical problems: the onboard use of liquid oxygen is prohibited, the use of small oxygen cylinders requires pre-flight agreement and, in case of airline oxygen supply, a pre-flight reservation needs to be done. POCs have advantages concerning safety, that is, no fire or projectile risk. While they do give an inexhaustible oxygen supply when connected to a power source there are disadvantages in terms of limited battery time, low-flow and low-pressure output.[5] We tested 2 POC

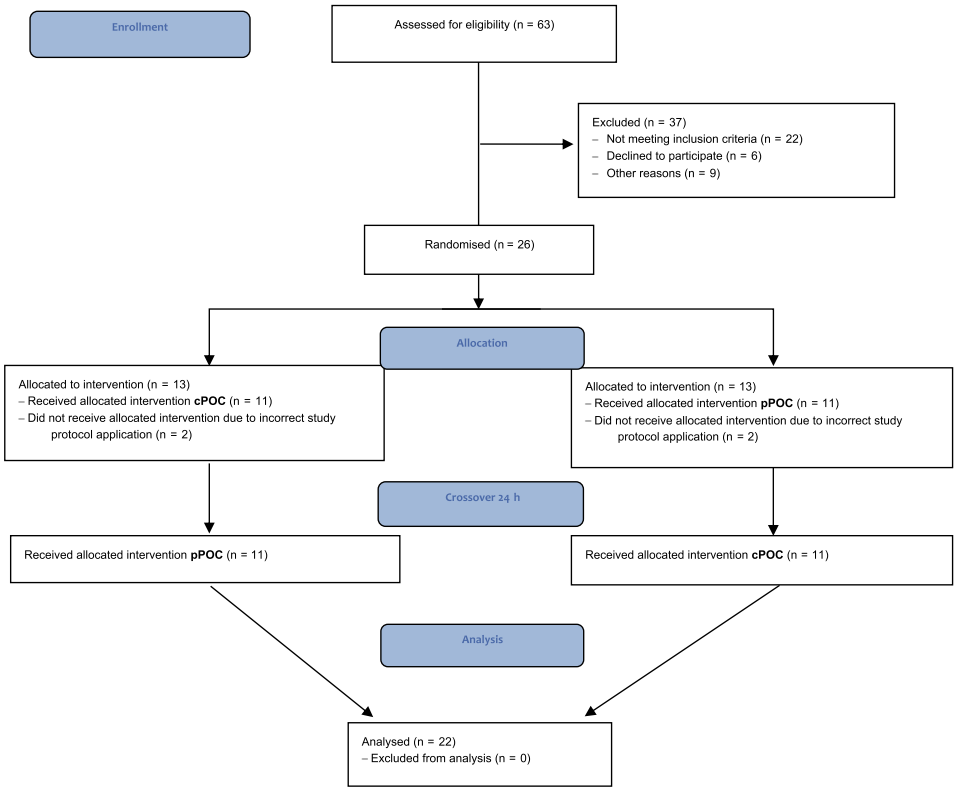

FIGURE 1 CONSORT flow diagram describing patient selection. Patients with SpO_2 ≤ 85% during induced hypoxia through HCT were allocated randomly in a crossover study design (study groups: cPOC vs pPOC). At 24 h, HCT was repeated and the still pending POC was tested

TABLE 1 Demographic and Clinical Data

	cPOC	pPOC
n	22	
Sex (f/m)	12/10	
Mean GA, wks (range)	30.4 (25-36)	
Mean corrected age, wks (range)	38.2 (34-59)	
Mean age, d (range)	58 (12-267)	
Mean weight, g (range)	2664 (1735-7400)	
Underlying disease	pb 15, pb + bpd 6, pb + bpd + ss 1	

Abbreviations: bpd, bronchopulmonary dysplasia; cPOC, continuous-flow portable oxygen concentrator; pb, premature birth; pPOC, pulsed-flow portable oxygen concentrator; ss, subglottic stenosis.

TABLE 2 Comparison of the tested POC devices (cPOC/pPOC)

	Mean	n	SD	95% CI	*P*-value*
Baseline SpO_2 cPOC, %[a]	99.4	22	0.734	(−0.05, 1.14)	.069
Baseline SpO_2 pPOC, %[a]	98.8	22	1.552		
Time to reach SpO_2 ≤ 85% cPOC, min[a]	8.7	22	3.5682	(−1.04, 2.15)	.477
Time to reach SpO_2 ≤ 85% pPOC, min[a]	8.2	22	2.7555		
Lowest SpO_2 during HCT cPOC, %[a]	77.2	22	4.320	(−5.10, 0.56)	.110
Lowest SpO_2 during HCT pPOC, %[a]	79.5	22	5.902		
Baseline HR cPOC, bpm[a]	160.3	22	21.830	(−11.58, 6.31)	.547
Baseline HR pPOC, bpm[a]	163	22	19.129		
Baseline FiO_2 cPOC, %[a]	20.9	22	0.5614	(−0.07, 0.55)	.119
Baseline FiO_2 pPOC,%[a]	20.7	22	0.3349		
Lowest FiO_2 during HCT cPOC, %[a]	15.2	22	0.6141	(−0.16, 0.28)	.580
Lowest FiO_2 during HCT pPOC, %[a]	15.1	22	0.4158		
Achieved SpO_2 using cPOC, %	98	22	3.251	(−2.91, 0.01)	.051
Achieved SpO_2 using pPOC, %	99.4	22	1.535		

Abbreviations: cPOC, continuous-flow portable oxygen concentrator; pPOC, pulsed-flow portable oxygen concentrator.

[a]Without POC operation.

*Level of significance: *P*-values < .05.

models performing HCT in ex-preterm infants where immediate hypoxia reversal was achieved in all cases. This pilot study demonstrates POCs capacity to generate sufficient oxygen to reverse HCT induced hypoxia, even in neonatal patients (ex-preterm patients who were full-term when HCT was performed). Fischer et al tested five POCs in COPD patients at a mountain altitude of 2650 metres compared with the standard oxygen system (*WS120, EMS Ltd.*) used by *Lufthansa*. All tested POCs achieved sufficient oxygen output observing a PaO_2 increase >20 mm Hg (2.55 kPa).[10] In 30 healthy adults, POC efficiency to revert hypobaric hypoxia was evaluated at 4267 metres compared with continuous-flow oxygen (cylinder). Pulsed-POCs were efficient albeit requiring increased pulse-dose volume to maintain equivalent SpO_2.[11] A crossover trial compared POCs to oxygen supply through nasal cannula in continuous-flow and oxygen conserving devices in 16 COPD patients undergoing induced hypobaric hypoxia where the continuous-flow or oxygen conserving device achieved similar PaO_2 values, whereas pulsed-POC (*Free-Style®; AirSep Corp*) required increased oxygen flow rates. They also advised that other types of POC may give different doses and concentrations.[12] Concerning POCs oxygen concentration capacity a bench study evaluated their use in simulated altitude (8000 m) under conditions of normobaric hypoxia (tent) and hypobaric hypoxia (chamber). Three out of four POCs achieved FiO_2 > 0.90 under hypobaric conditions. Nevertheless, under normobaric conditions FiO_2 was < 0.76; however, the testing method was questioned by the author suspecting excessively high nitrogen concentration in the gas mixture introduced in the tent.[13]

To our knowledge, this is the first time POCs have been tested in paediatric age subjects under simulated altitude conditions while performing HCT. We opted for a crossover study design to limit interpersonal variation. Our results suggest POCs are effective at simulated altitude. All our patients showed immediate hypoxic recovery by POC oxygen administration at preestablished flow settings without associated adverse events.

We observed that pPOCs were effective even in our 'extreme patient group' in terms of weight and inspiratory capacity (no backup

mode activation in any patient). In elder children, POCs breath sensing should be guaranteed because of improved inspiratory capacity in this age group. In our pilot study, we tested 2 different POC devices in a limited number of patients and only for a short time (20 minutes); therefore, we are no able to assure their effectiveness for longer periods of time including feeding and sleeping periods. The amounts of generated oxygen during inspiration differ between pPOC devices. In a bench study, significant differences in oxygen delivery among different POCs at identical pulse flow settings were observed.[14] Therefore, we recommend testing the device before onboard use in each patient.

Limitations of our trial include time and conditions of testing (awake, not feeding) and the lack of comparison to hypobaric HCT or a real inflight scenario where FiO_2 output and POC performance may be reduced. We did not assessed patient's FiO_2 level and, therefore, the impact on hyperoxic lung injury (increased risk on flow rates ≥ 2 L/min) and lung development remains unclear.[15] As we assessed POCs for onboard use, inflight oxygen exposure is only for a short time period. Conventional oxygen supply provided by airlines is given on preestablished flow rate between 2 and 4 L/min. Therefore, we do not consider 'short term' POC use as a risk factor for hyperoxic lung injury. We tested POCs on a preestablished flow rate without individualising between patients. We cannot exclude that some of our patients may have shown a positive hypoxia reversal on reduced gas flows and consequently decreased FiO_2. Further, the respiratory rate was not monitored, and although this may show variability among the tested subjects, it does not seem to influence the final results.

5 | CONCLUSION

Both POC devices showed the capacity to generate sufficient oxygen to reverse HCT induced hypoxia. Although pPOCs are not recommended in paediatric age, the results of our crossover trial, suggest that they may be effective even in neonatal age without associated adverse events. Following this pilot study, more research will be required (especially concerning pPOC use) to verify our results and to establish recommendations for their use in paediatric age.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare regarding the publication of this article.

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SUMMARY OF FINDINGS

13 SUMMARY OF FINDINGS

13.1 RESEARCH PROJECT 1.

Summary of the main results obtained from Research Project 1.	
+	46 of 51 children (90%) passed HCT after 24 hours without oxygen supply and were considered fit-to-fly.
+	Of those 5 of 51 (10%) who did not pass, HCT was repeated after 48 hours and all (100%) passed HCT.
+	Patients who failed HCT within the first 24 hours showed lower FEV1 values compared to the group who passed HCT (FEV1 69% vs 89%, p.038).
+	No differences were found in SaO_2 before HCT, days of hospitalization, required oxygen supply, and maximum FiO_2. Therefore, these items are not reliable concerning inflight risk assessment.
-	Limitations: HCT was not performed under hypobaric conditions, which is considered as the gold standard assessing inflight risk. PaO_2 values are not registered. This painful test is not used habitually in children because of ethical concerns.

FEV1: forced expiratory volume in 1 second; PaO_2: arterial partial pressure of oxygen; SaO_2: arterial oxygen saturation; HCT: Hypoxic Challenge Testing

13.2 RESEARCH PROJECT 2.

Summary of the main results obtained from Research Project 2.	
+	Both tested POCs achieved immediate hypoxia reversal at standard flow in all cases without associating adverse events achieving mean maximum SaO_2 of 98% (cPOC) and 99.45% (pPOC)
+	No significant difference was observed between ex-preterm patients with or without BPD concerning POC response.
+	pPOCs (pulsed-flow) are able to detect patient´s inspiration even in our "extreme patient group" (ex-preterm patients who were tested near term or term age).
-	Limitations: include time and conditions of testing. Our patients were tested awake without feeding. Patients who sleep or eat may show a different HCT response. HCT was not performed under hypobaric conditions, which is considered as the gold standard assessing inflight risk. PaO_2 values are not registered. This painful test is not used habitually in children because of ethical concerns.

PaO_2: arterial partial pressure of oxygen; cPOC: continuous-flow portable oxygen concentrator; pPOC: pulsed-flow portable oxygen concentrator; SaO_2: arterial oxygen saturation; HCT: Hypoxic Challenge Testing

DISCUSSION

14 DISCUSSION

14.1 RESEARCH PROJECT 1.

According to our results, children hospitalized due to acute asthma exacerbation, who do not require oxygen supply for 48 hours are considered “fit-to-fly” without need for a pre-flight test. There are no similar studies in current literature that respond to the question when a patient is considered to have a low risk of inflight hypoxia in case of hospital admission due to the described characteristics. In general, it is recommended that patients with severe or poorly controlled asthma avoid flying and in case of hospital admission the trip should be delayed until the patient is stable and well controlled with medication or postpone the planned flight for 2 weeks after respiratory exacerbation.[18]

Further predictive equations using PaO_2 levels at sea level and afterwards under simulated inflight conditions were tested in adults with COPD including lung function variables in order to predict the hypoxic response.[29,40] However, these studies do not include children and their ability to predict the response has been questioned as up to 33% of the formulas do not correctly predict the test.[30] The main predictor of PaO_2 during flight is extracted from formulas made in patients with COPD. However, as the reliability of these equations remain unclear they are not routinely used in clinical practice in the UK.[41]

Studies carried out in cystic fibrosis patients including children showed that FEV1 values < 50% are associated with inflight hypoxia however, given the specific characteristics of this pathology, the results are not applicable to our group or to patients without chronic lung pathology suffering from acute exacerbation.[42] The objective of these studies is to find clinical variables that are able to predict the response to a hypoxic environment. In our study, the values of FEV1 were lower in the group that failed HCT during the first 24 hours without oxygen supply but did not prove to be a good predictor. Pulmonary function in the first 24 hours after the withdrawal of oxygen therapy presents in most cases, values with mild impairment, which suggests a multifactorial etiology of hypoxia that includes other causes added to the obstruction such as mucus and ventilation-perfusion mismatch.

Related to the importance of clinical symptoms, in a prospective study, 82 patients with COPD who had a previous flight underwent HCT. They concluded that the results of the test cannot be related to the symptoms due to inter-individual differences, but nevertheless they observed that a hypoxia during the simulation is a risk factor for presenting symptoms.[43]

Our study represents the first report evaluating asthmatic patients hospitalized for severe asthmatic crisis performing HCT for inflight hypoxic risk assessment. The sample includes patients with very high oxygen requirements during admission (up to FiO_2 1), who have not shown a greater risk of hypoxemia during HCT, which makes the results more consistent.

Limitations: (1) HCT was not performed under hypobaric conditions which is considered the gold standard. Hypobaric chambers are rarely available and therefore not routinely used in pre-flight assessment. Although the results regarding hypoxia in previous studies are similar, symptoms might appear caused by the lower pressure in the cabin of the aircraft. Air trapping was unlikely given the pulmonary function values from our patients. (2) Hypoxia was assessed by pulsoximetry (SaO_2) and not by invasive arterial determination of PaO_2. Although this value is not as accurate, we have seen a strong correlation (r = 0.81) between these values.[43] In addition, the performance of arterial blood gases testing is not a usual procedure in children and the recommendation of the guidelines is to perform the test with SaO_2 monitoring. (3) It should be taken into account that this study only includes patients hospitalized for an acute asthma exacerbation, and that the results may not be applicable to the first days of an outpatient exacerbation. (4) Although HCT is assumed to be a reliable predictor of the patient's hypoxic response during the flight, the results have not been compared with a SaO_2 under real flight conditions as has been done in other studies. Thus there is a lack of comparison to a real inflight scenario.[42]

14.2 RESEARCH PROJECT 2.

Despite onboard POCs being widely available there is lack of evidence about their effectiveness and safety during air travel especially in pediatric age patients. *Fischer et al.* tested five POCs (*Inogen One®* and *Eclipse 3®* included) in COPD patients at a mountain altitude of 2650 meters compared to the standard oxygen system (WS120, EMS Ltd., Germany) used by Lufthansa. All tested POCs achieved sufficient oxygen output observing an PaO_2 increase > 20 mmHg (2.55 kPa).[44] *Blakeman et al.* assessed POCs efficiency (*Eclipse 3®* included) to revert hypobaric hypoxia at 4267 meters compared to continuous-flow oxygen from a cylinder in 30 healthy adults. pPOCs were efficient albeit requiring increased pulse dose volume to maintain equivalent SaO_2 compared to continuous-flow cylinders.[45] *Akerø et al.* tested in a randomised crossover trial 16 COPD patients undergoing induced hypobaric hypoxia through a chamber. Oxygen was given by nasal cannula with continuous flow (compressed gaseous oxygen), an oxygen-conserving device, and a pPOC. Oxygen on continuous flow and the tested oxygen conserving device achieved similar PaO_2 values, whereas pulsed-POC *(Free-Style®; AirSep Corp; Buffalo, New York)* required increased oxygen flow rates for delivery of a similar PaO_2. They also advised that other types of POCs may give other doses and concentrations.[31] Concerning POCs oxygen concentration capacity a bench study evaluated their use in simulated altitude up to 8000 m (*Eclipse 3®* included) under conditions of normobaric hypoxia (tent) and hypobaric hypoxia (chamber). Three out of four POCs achieved FiO_2 > 90% under hypobaric conditions. Nevertheless under normobaric conditions FiO_2 was < 76% however the testing method was questioned by the author suspecting excessively high nitrogen concentration in the gas mixture introduced in the tent.[37]

To our knowledge this study assessed POCs for the first time by performing HCT in pediatric age patients; the recommended method for inflight hypoxic risk evaluation according to BTS guidelines.[18] We opted for a crossover study design to limit interpersonal variation. Limitations include time and conditions of testing (e.g. awake, no feeding) and lack of comparison to a real inflight scenario.

All our patients showed immediate hypoxic recovery by POC oxygen administration at standard flow without associated adverse events in any of the tested patients. In this trial pPOCs were able to detect patient´s inspiration even in our “extreme patient group” in terms of weight and respiratory capacity (ex-preterm patients who were tested near term or term age). In elder children POCs patient sensing should be guaranteed because of improved respiratory capacity in this age group. Concerning pPOCs, the amount of generated oxygen in each breath varies according to the model. In a bench study, significant differences in oxygen delivery among different POCs at identical pulse flow settings were observed.[46] Therefore we recommend testing the device before onboard use in each patient.

Limitations: (1) Time and conditions of testing: Patients were awake without being fed. (2) Lack of comparison to hypobaric HCT or a real inflight scenario where FiO_2 output and POC performance may be

reduced. (3) We did not assessed patient´s FiO_2 level and therefore the impact on hyperoxic lung injury and lung development remains unclear. As we assessed POCs for onboard use, inflight oxygen exposition is only for a short time period. Conventional oxygen supply provided by airlines is given on preestablished flow rate between 2-4 l/min. Therefore, we do not consider “short term” POC use as a risk factor for hyperoxic lung injury. (4) We tested POCs on a preestablished flow rate without individualizing between patients. We cannot exclude that some of our patients may have shown a positive hypoxia reversal on reduced gas flows and consequently decreased FiO_2.

CONCLUSION & FUTURE RESEARCH

15 CONCLUSIONS

15.1 1. RESEARCH PROJECT 1.

Patients with acute respiratory failure due to asthmatic exacerbation requiring admission to hospital pass the pre-flight HCT in the first 48 hours after oxygen supply removal. This data may be included in current pre-flight assessment guidelines and patient briefing.

15.2 2. RESEARCH PROJECT 2.

Both POC devices showed the capacity to generate sufficient oxygen to reverse HCT induced hypoxia. Although pPOCs are not recommended in paediatric age, our crossover trial suggest they are effective even in neonatal age without associated adverse events. Following this pilot study, more research will be needed to verify our results including a larger sample size and a longer HCT duration.

16 FUTURE RESEARCH

Extended POC use: Through this RCT we proved the effectiveness of POCs under induced hypoxia, which is considered an “extreme” condition. However, in remote areas or in developing countries where access to electricity is not assured and the availability of oxygen bottles may be limited or absent, the use of a POC may be considered for treatment of respiratory distress or for minor surgical interventions.

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APPENDIX

18 APPENDIX

18.1 DATA COLLECTION LOGBOOK (DCL) – SPANISH

Utilidad de los concentradores de oxigeno portátiles para corrección de hipoxia en simulación de altitud

Fecha realización:
Nombre:
NHC:
Fecha de nacimiento:

Edad:
Peso (Kg):
Talla (cm):
Resumen/Antecedentes principales:

Se realiza test de hipoxia en cabina de pletismografía con registro de pulsioximetría continua.

	SaO_2	FC	FiO_2
Inicio			
3 min			
5 min			
8 min			
10 min			
12 min			
15 min			
18 min			
20 min			

Pausas de apnea o bradicardia: _____

Corrección con cCOP Eclipse 3 (continuos flow): _____

	SaO_2	FC	FiO_2
Inicio			
3 min			
5 min			

Conclusión: _____

Corrección con pCOP Inogen One G3 (pulsed-flow): _____

	SaO_2	FC	FiO_2
Inicio			
3 min			
5 min			

Conclusión: _____

18.2 INFORMED CONSENT (IC) - *SPANISH*

CONSENTIMIENTO INFORMADO PARA LA REALIZACIÓN DE PROYECTOS DE INVESTIGACIÓN

Utilidad de los concentradores de oxigeno portátiles para corrección de hipoxia en simulación de altitud

Código del Estudio: cop2016

Yo (nombre y apellidos) …….. de ..... años en calidad de……. (relación con el participante) de…….(nombre y apellidos del participante) consiento

- ☐ He leído la hoja de información que se me ha entregado.
- ☐ He podido hacer preguntas sobre el estudio.
- ☐ He recibido suficiente información sobre el estudio.
- ☐ He hablado con: .....(nombre del investigador)
- ☐ Comprendo que la participación del menor es voluntaria.

- ☐ Comprendo que puedo retirar el menor del estudio:
  1º Cuando quiera
  2º Sin tener que dar explicaciones.
  3º Sin que esto repercuta en mis cuidados médicos.
- ☐ Comprendo que si decido retirar el menor del estudio los resultados obtenidos hasta ese momento podrán seguir siendo utilizados pero que no se incorporarán nuevos datos.
- ☐ Comprendo que tengo los derechos de acceso, rectificación, cancelación y oposición a mis datos de carácter personal de acuerdo con lo dispuesto en la Ley Orgánica 15/1999 de protección de datos de carácter personal.

- ☐ Presto libremente mi conformidad para dejar participar al menor en el estudio y doy mi consentimiento para el acceso y utilización de mis datos en las condiciones detalladas en la hoja de información.

Firma
Representante legal menor

Firma del investigador:

Nombre:
Fecha:

Nombre:
Fecha: